

LETTER-TO-THE-EDITOR

Prevalence of Multidrug-resistant *Shigella* Isolated in Malaysia

Sir,

Shigellosis, a disease caused by *Shigella* spp., is endemic in Malaysia. Its low infective dose and ease of spread through person-to-person transmission by the faecal-oral route make this infection difficult to control in outbreak situations. Antimicrobial therapy is recommended for shigellosis because it can shorten the severity and duration of illness, reduce shedding of the organism, and prevent secondary complications and deaths. However, due to the global emergence of drug resistance, the choices of antimicrobial agents for empiric therapy for shigellosis are now limited (1). Although antimicrobial resistance of *Shigella* spp. is well-documented in many countries (2-4), there is a lack of such documentation in Malaysia. Hence, the study was undertaken to determine the antimicrobial resistance patterns of the Malaysian strains of *Shigella* spp. This study, to the best of our knowledge, is the first report on the antimicrobial resistance of *Shigella* spp. in Malaysia.

One hundred clinical strains (stools, n=98; blood, n=2) of *Shigella* spp. isolated during 1997-2000 from sporadic cases of endemic shigellosis in different parts of Malaysia, were studied. *Shigella* spp. were identified by biochemical and serological tests at the Institute for Medical Research, Kuala Lumpur, Malaysia. Antimicrobial susceptibility tests were determined by the Bauer-Kirby disc-diffusion method (5). Antibiotic disks (Oxoid, UK) of 10 antimicrobial agents: ampicillin (Amp), amikacin (An), chloramphenicol (Chl), ciprofloxacin (Cip), ceftriaxone (Cro), kanamycin (Kan), streptomycin (Str), tetracycline (Tet), trimethoprim (Tmp), and trimethoprim-sulphamethoxazole (SxT) were tested. Zones of inhibition were recorded in millimetres and interpreted as sensitive, intermediate, or resistant according to the instructions of the manufacturer.

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Minimum inhibitory concentrations (MICs) of ampicillin, chloramphenicol, streptomycin, tetracycline, trimethoprim, and trimethoprim-sulphamethoxazole for selected strains were determined by the agar dilution technique according to the recommendations of the National Committee for Clinical Laboratory Standards [6]. *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 29213, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control organisms.

Of the 100 clinical strains of *Shigella* tested, 88%, 11%, and 1% were *Shigella flexneri*, *S. dysenteriae*, and *S. boydii* respectively. Nine serotypes—1a (n=3), 1b (n=40), 2a (n=27), 3a (n=20), 3b (n=1), 3c (n=9), 4a (n=10), 6 (n=1), and y (n=2)—belonged to *S. flexneri*. Two serotypes of *S. dysenteriae*—type 2 (n=10) and 6 (n=1)—were isolated, while the only *S. boydii* isolate was of serotype 6. As reported in other developing countries, *S. flexneri* is also the most common species in Malaysia (1).

Twenty-seven percent of all *Shigella* isolates tested showed full sensitivity, while 73% were highly resistant to at least one antibiotic. Overall, 72%, 57%, 56%, 55%, 41%, 34%, and 8% of *Shigella* spp. were resistant to streptomycin, tetracycline, ampicillin, chloramphenicol, trimethoprim, trimethoprim-sulphamethoxazole, and kanamycin respectively. All the strains were susceptible to ciprofloxacin, ceftriaxone, and amikacin, except 3 strains of *S. flexneri* serotype 1b, which had intermediate susceptibility to amikacin. All the 10 *S. dysenteriae* serotype 2 were resistant to streptomycin, while *S. dysenteriae* serotype 6 and *S. boydii* strains were fully sensitive.

Species-specific trends of drug resistance were analyzed for *S. flexneri*. The resistance rates of *S. flexneri* to trimethoprim and trimethoprim-sulphamethoxazole steadily increased from 9.1% in 1997 to 64.3% in 2000. Resistance to kanamycin was first observed in 1998 (5.7%) and then increased from 10.0% to 21.4% in 1999 and 2000 respectively. The high rate of resistance to trimethoprim-sulphamethoxazole and trimethoprim and

the emergence of resistance to kanamycin suggest that the routine use of these drugs in treating patients with suspected shigellosis should be reviewed. Resistance of *S. flexneri* to ampicillin, chloramphenicol, streptomycin, and tetracycline remained high from 1997 through 2000 with only minor fluctuations. Such high resistance rates have been reported in Israel (2), Northeast Brazil (3), Hong Kong (4), Egypt (7), and elsewhere (3). The continuous overuse of these antimicrobial agents in the treatment of shigellosis probably sustained these resistant traits.

Multidrug resistance rates of *S. flexneri* were high too, since 71.6% of the strains were resistant to at least two antimicrobial agents. Twelve resistant phenotypes were defined: phenotype I (Str^r) (1%), phenotype II (Kan^r) (1%), phenotype III (Str^r Kan^r) (1%), phenotype IV (Str^r Tmp^r SxT^r) (2%), phenotype V (Str^r Tmp^r Te^r) (1%), phenotype VI (Str^r Amp^r Chl^r) (1%), phenotype VII (Str^r Amp^r Tet^r Chl^r) (21%), phenotype VIII (Str^r Tmp^r, SxT^r Tet^r) (1%), phenotype IX (Str^r Tmp^r, Amp^r Tet^r, Chl^r) (7%), phenotype X (Str^r Tmp^r Amp^r SxT^r Tet^r) (1%), phenotype XI (Str^r Tmp^r Amp^r SxT^r Tet^r Chl^r) (27%), and phenotype XII (Str^r Tmp^r Amp^r SxT^r Tet^r Chl^r Kan^r) (7%).

The MICs of selected *S. flexneri* strains showed a high percentage of resistance to streptomycin (91.7%), tetracycline (70.8%), and chloramphenicol (65.4%). The values of MICs for ampicillin and chloramphenicol (≥ 64 µg/mL and ≥ 128 µg/mL respectively) were similar to those reported in Hong Kong (4). MIC₉₀ for streptomycin, trimethoprim, and trimethoprim-sulphamethoxazole were strikingly high (≥ 1024 µg/mL). The high MICs could have a profound impact on the treatment of shigellosis because certain antimicrobial agents, such as chloramphenicol, are toxic to human cells at high concentrations.

Isolates of *Shigella* in Malaysia are still sensitive to ciprofloxacin, ceftriaxone, and amikacin. The use of ciprofloxacin in children is debatable. Ceftriaxone is a good choice of drug for the treatment of shigellosis since cephalosporins are an effective agent against *Shigella* species and also safe (2). Evidence suggests that resistance to amikacin was developing among *S. flexneri* type strains in Malaysia as three strains of *S. flexneri* serotype 1b showed intermediate susceptibility to amikacin. Amikacin is a modified form of kanamycin A, which has a substituted aminobutyl in the amino group at position 1 in the 2-deoxystreptamine ring, and this enhances its resistance to some types of

aminoglycoside-modifying enzymes (7). The emergence of resistance of *S. flexneri* to kanamycin may suggest the possibility of *Shigella* spp. in Malaysia acquiring resistance to amikacin too. Thus, the use of amikacin in routine treatment of shigellosis should be carried out either in a controlled manner or in conjunction with other antimicrobial agents to delay the development of resistance.

Our study has shown that resistance of *S. flexneri* to chloramphenicol was always linked to resistance to ampicillin, tetracycline, and streptomycin. This observation suggests that genes encoding the resistance to these antimicrobial agents could be linked together as a group or a cassette. This assumption was supported by a study by Casalino and colleagues who showed that genes encoding for resistance to ampicillin, chloramphenicol, tetracycline, and spectinomycin formed a linkage group located on the chromosome (8).

The endemicity and prevalence of high resistance rates of *Shigella* spp. necessitate better control measures, such as improving public hygiene, preventing excessive use of existing antimicrobial agents, or the development of newer, more broad-spectrum antimicrobial agents.

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